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Hopf bifurcation analysis in a model of oscillatory gene expression with delay

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The dynamics of a gene expression model with time delay are investigated. The investigation confirms that a Hopf bifurcation occurs due to the existence of stability switches when the delay varies. An explicit algorithm for determining the direction of the Hopf bifurcations and the stability of the bifurcating periodic solutions has been derived by using the theory of the centre manifold and the normal forms method. The global existence of periodic solutions has been established using a global Hopf bifurcation result by Wu and a Bendixson criterion for higher-dimensional ordinary differential equations due to Li and Muldowney.

1. Introduction

The feedback inhibition of gene expression is a widespread phenomenon in molecular biology. The feedback in eukaryotic cells involves time delays resulting from transcription, transcript splicing and processing and protein synthesis. Generally, such delays will result in oscillatory messenger ribonucleic acid (mRNA) and protein expression [11].

The concept of oscillatory gene expression driven by negative feedback loops was first predicted by Goodwin [4]. Since then, oscillations in biological systems with delay have attracted considerable attention [10–15]. Although some mathematical models incorporating delayed feedback have been studied [10, 11], these models cannot demonstrate whether transcriptional and translational time delay has a significant impact on the dynamics of gene expression.

The best-characterized system centres on the induction of oscillatory expression of the basic helix–loop–helix transcription factor HES1 in cultured murine cell lines stimulated by serum [7]. HES1 represses the transcription of its own gene through direct binding to regulatory sequences in the HES1 promoter [7] (see figure 1). Let $M(t)$ be the concentration of HES1 mRNA at time t and let $P(t)$ be the concentration of HES1 protein at time t. Then the rate of change of $M(t)$ and $P(t)$ might be supposed to obey the equations

$$\dot{M}(t) = af(P(t-\tau)) - \mu M(t), \qquad \dot{P}(t) = bM(t) - dP(t), \tag{1.1}$$

where $a > 0$ is the basal rate of transcript initiation in the absence of the associated protein, $b > 0$ is the rate at which the HES1 protein is produced from HES1 mRNA, $\mu > 0$ and $d > 0$ are the rates of degradation of HES1 mRNA and HES1

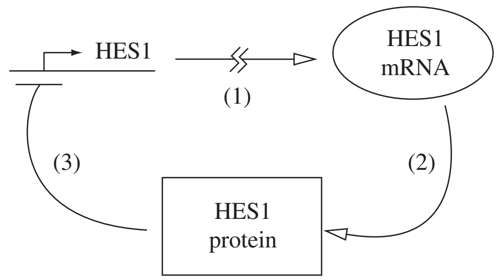

Figure 1. Schematic representation of the delayed HES1 feedback loop. (1) Transcript elongation, splicing, processing and export from the nucleus to the cytoplasm. (2) Synthesis of HES1 protein by translation of HES1 mRNA. A translational delay can be absorbed into the transcriptional delay. (3) Repression of transcript initiation from the HES1 gene, through the binding of HES1 dimers to the promoter.

protein, respectively, and $f(P(t-\tau))$ is the rate of production of new HES1 mRNA molecules, which is assumed to be a decreasing function. Throughout this paper, we assume that

$$f(P(t-\tau)) = \frac{1}{1 + (P(t-\tau)/P_0)^n},$$

where $P_0 > 0$ is a reference concentration of protein $n > 1$.

Monk [14] provided direct evidence that transcriptional delays can drive oscillatory gene activity and highlighted the importance of considering delays when analysing genetic regulatory networks. Lewis [8] showed that the period of oscillation could be determined by the transcriptional and translational delays.

Recently, Verdugo and Rand [22] obtained a critical time delay beyond which a periodic motion is born in a Hopf bifurcation, and further demonstrated that the Hopf bifurcation may not occur if the rates of degradation are too large under the condition that $\mu = d$.

In the present paper, we provide a detailed analysis of this model. We investigate not only the stability of the positive fixed point and the existence of the local Hopf bifurcation, but also the direction of the Hopf bifurcation and the stability of the bifurcating periodic solutions and the continuation of the Hopf branches. In order to obtain the first global Hopf branch to show that an eight-dimensional ordinary differential equation (ODE) has no periodic solutions, we use the Bendixson criterion for higher-dimensional ODEs due to Li and Muldowney [9]. Since the model with delay possesses more complex dynamics than the ODE, the mathematical investigation of this model would be interesting. For instance, the model without delay has no periodic solutions, but the number of periodic solutions of the model increases as the delay increases.

In recent years, there have been several papers on the global Hopf bifurcation of delay differential equations by using the global Hopf bifurcation theorem due to Wu [32] and, hence, we refer the reader to [2, 3, 16, 18–21, 23–34] and the references cited therein.

The remainder of this paper is organized as follows. In § 2 we employ a result from Ruan and Wei [17] to analyse the distribution of the characteristic equation associated with this model, and obtain the existence of the local Hopf bifurcation. In § 3 the direction of the Hopf bifurcation and the stability of the bifurcating periodic solutions are determined by using the normal form theory and centre manifold argument presented in [6]. In § 4 global Hopf bifurcations are established. Some numerical simulation examples are given in order to illustrate the results obtained in § 5.

2. Stability and local Hopf bifurcation

In this section we employ the result due to Ruan and Wei [17] to study the stability of the positive equilibrium and existence of local Hopf bifurcation.

By setting $m = M/a$, $p = P/ab$ and $p_0 = P_0/ab$, system (1.1) can be expressed as follows:

$$\dot{m}(t) = \frac{1}{1 + (p(t-\tau)/p_0)^n} - \mu m(t), \qquad \dot{p}(t) = m(t) - dp(t). \tag{2.1}$$

If (m^*, p^*) is an equilibrium of system (2.1), it satisfies

$$\mu m = \frac{1}{1 + (p/p_0)^n}, \qquad m = dp. \tag{2.2}$$

This leads to

$$p^{n+1} + p_0^n p - \frac{p_0^n}{\mu d} = 0.$$

Let

$$G(p) = p^{n+1} + p_0^n p - \frac{p_0^n}{\mu d}.$$

Then

$$G(0) = -\frac{p_0^n}{\mu d} < 0 \quad \text{and} \quad G'(p) = (n+1)p^n + p_0^n > 0 \quad \text{for any } p > 0.$$

This implies that the system (2.1) has a unique positive equilibrium, denoted by (m^*, p^*). Clearly, $m^* < 1/\mu$ and $p^* < 1/(\mu d)$.

Let $m(t) = m(t) - m^*$ and $p(t) = p(t) - p^*$. Then system (2.1) becomes

$$\left.\begin{aligned} \dot{m}(t) &= \frac{1}{1 + ((p(t-\tau) + p^*)/p_0)^n} - \mu(m(t) + m^*), \\ \dot{p}(t) &= m(t) - dp(t). \end{aligned}\right\} \tag{2.3}$$

The linearization of (2.3) around (m^*, p^*) is given by

$$\dot{m}(t) = -Kp(t-\tau) - \mu m(t), \qquad \dot{p}(t) = m(t) - dp(t), \tag{2.4}$$

where $K = n\beta/[p^*(1+\beta)^2]$ and $\beta = (p^*/p_0)^n$, whose characteristic equation is

$$\lambda^2 + (\mu + d)\lambda + \mu d + K\mathrm{e}^{-\lambda\tau} = 0. \tag{2.5}$$

Now, let us consider the distribution of the roots of (2.5).

LEMMA 2.1. *Assume that*

$$K > \mu d \tag{H1}$$

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is satisfied. Then (2.5) has a pair of purely imaginary roots $\pm \mathrm{i}\omega_0$ *when* $\tau = \tau_j$, *where*

$$\left.\begin{aligned} \omega_0 &= (\tfrac{1}{2}[-\mu^2 - d^2 + \sqrt{(\mu^2+d^2)^2 - 4(\mu^2 d^2 - K^2)}])^{1/2}, \\ \tau_j &= \frac{1}{\omega_0}\left[\arccos\frac{\omega_0^2 - \mu d}{K} + 2j\pi\right], \quad j = 0, 1, 2, \dots. \end{aligned}\right\} \tag{2.6}$$

Proof. Let $\mathrm{i}\omega$ $(\omega > 0)$ be a root of (2.5). Then

$$-\omega^2 + \mathrm{i}(\mu + d)\omega + \mu d + K(\cos\omega\tau - \mathrm{i}\sin\omega\tau) = 0.$$

The separation of the real and imaginary parts yields

$$\left.\begin{aligned} -\omega^2 + \mu d + K\cos\omega\tau = 0, \\ -(\mu+d)\omega + K\sin\omega\tau = 0. \end{aligned}\right\} \tag{2.7}$$

Hence

$$\omega^2 = \tfrac{1}{2}[-\mu^2 - d^2 \pm \sqrt{(\mu^2+d^2)^2 - 4(\mu^2 d^2 - K^2)}].$$

Clearly, (H1) implies that

$$\omega_0 = (\tfrac{1}{2}[-\mu^2 - d^2 + \sqrt{(\mu^2+d^2)^2 - 4(\mu^2 d^2 - K^2)}])^{1/2},$$

and, hence,

$$\tau_0 = \frac{1}{\omega_0}\arccos\frac{\omega_0^2 - \mu d}{K}.$$

Define $\tau_j = \tau_0 + 2j\pi/\omega_0$, $j = 0, 1, 2, \dots$. Then (τ_j, ω_0) solves (2.7). This means that $\mathrm{i}\omega_0$ is a root of (2.5) when $\tau = \tau_j$, $j = 0, 1, 2, \dots$. This completes the proof. □

Let $\lambda(\tau) = \alpha(\tau) + \mathrm{i}\omega(\tau)$ be the root of (2.5) satisfying $\alpha(\tau_j) = 0$ and $\omega(\tau_j) = \omega_0$, $j = 0, 1, 2, \dots$.

Lemma 2.2. *If (H1) holds, then* $\alpha'(\tau_j) > 0$.

Proof. By substituting $\lambda(\tau)$ into (2.5) and differentiating both sides of the equation with respect to τ, we obtain

$$\alpha'(\tau_j) = \frac{\omega^2(2\omega^2 + \mu^2 + d^2)}{\Delta},$$

where $\Delta = [\mu + d - \tau\omega^2 + \tau\mu d]^2 + [2\omega + (\mu + d)\tau\omega]^2$. The conclusion follows. □

Lemma 2.3.

(i) *If* $K < \mu d$ *holds, then all roots of (2.5) have negative real parts.*

(ii) *If (H1) holds, then there exist* $\tau_0 < \tau_1 < \tau_2 < \cdots$ *such that all the roots of (2.5) have negative real parts, when* $\tau \in [0, \tau_0)$ *and (2.5) has* $2(j+1)$ *roots with positive real parts when* $\tau \in (\tau_j, \tau_{j+1})$, *where* τ_j *is defined as in (2.6).*

Proof. When $\tau = 0$, (2.5) becomes

$$\lambda^2 + (\mu + d)\lambda + \mu d + K = 0. \tag{2.8}$$

Clearly, the roots of (2.8) have negative real parts. The ω_0 defined in (2.6) is meaningless when $K < \mu d$, which means that (2.5) has no roots appearing on the imaginary axis. Hence, the conclusion of (i) follows. By using lemmas 2.1 and 2.2 and [17, corollary 2.4], the conclusion of (ii) follows under the condition (H1). □

Applying lemmas 2.2, 2.3 and the Hopf bifurcation theorem of functional differential equations [5], we have the following results.

THEOREM 2.4.

(i) *If $K < \mu d$, (m^*, p^*) is asymptotically stable for any $\tau > 0$.*

(ii) *Suppose that (H1) is satisfied. Then (m^*, p^*) is asymptotically stable for $\tau \in [0, \tau_0)$, and unstable for $\tau > \tau_0$. System (2.1) undergoes a Hopf bifurcation at (m^*, p^*) when $\tau = \tau_j$ for $j = 0, 1, 2, \dots,$ where τ_j is defined as in (2.6).*

3. Direction and stability of the Hopf bifurcation

In the previous section, we obtained conditions for Hopf bifurcations to occur when $\tau = \tau_j$, $j = 0, 1, 2, \dots$. In this section we investigate the direction of the Hopf bifurcation and the stability of the bifurcating periodic solutions when $\tau = \tau_0$, using techniques of the normal form and centre manifold theory (see, for example, [6]).

For convenience, let $t = s\tau$, and still denote time t. Then system (2.3) can be rewritten as

$$\left.\begin{aligned} \dot{m}(t) &= \frac{\tau}{1 + ((p(t-1) + p^*)/p_0)^n} - \tau\mu(m(t) + m^*), \\ \dot{p}(t) &= \tau m(t) - \tau d p(t). \end{aligned}\right\} \tag{3.1}$$

Correspondingly, the characteristic equation (2.5) becomes

$$v^2 + \tau(\mu + d)v + \tau^2\mu d + \tau^2 K \mathrm{e}^{-v} = 0, \tag{3.2}$$

with $v = \tau\lambda$ for $\tau \neq 0$. From lemma 2.3(ii) we know that if (H1) holds and $\tau = \tau_0$, all roots of (3.2) except $\pm \mathrm{i}\tau_0\omega_0$ have negative real parts. Furthermore, by lemma 2.2, the root of (3.2),

$$v(\tau) = \tau\alpha(\tau) + \mathrm{i}\tau\omega(\tau),$$

with $\alpha(\tau_0) = 0$ and $\omega(\tau_0) = \omega_0$ satisfies

$$\left.\frac{\mathrm{d}(\tau\alpha(\tau))}{\mathrm{d}\tau}\right|_{\tau=\tau_0} = \tau_0\alpha'(\tau_0) > 0.$$

Set $\tau = \tau_0 + \alpha$, $\alpha \in \mathbb{R}$. Then $\alpha = 0$ is the Hopf bifurcation value of system (3.1). Then rewrite (3.1) as

$$\left.\begin{aligned} \dot{m}(t) &= (\tau_0 + \alpha)[-Kp(t-1) + a_2 p^2(t-1) + a_3 p^3(t-1) - \mu m(t)] + O(p^4), \\ \dot{p}(t) &= (\tau_0 + \alpha)(m(t) - d p(t)), \end{aligned}\right\} \tag{3.3}$$

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where

$$a_2 = \frac{\beta n(\beta n - n + \beta + 1)}{2(\beta + 1)^3 p^{*2}},$$

$$a_3 = \frac{\beta n[6\beta n(1+\beta)(n-1) - (n-1)(n-2)(1+\beta)^2 - 6(\beta n)^2]}{6(\beta+1)^4 p^{*3}}.$$

Choose the phase space as $\mathcal{C} = C([-1,0], \mathbb{R}^2)$. For any $\phi = (\phi_1, \phi_2)^{\mathrm{T}} \in \mathcal{C}$, let

$$\begin{aligned} L_\alpha(\phi) &= (\tau_0 + \alpha) \begin{pmatrix} -\mu & 0 \\ 1 & -d \end{pmatrix} \begin{pmatrix} \phi_1(0) \\ \phi_2(0) \end{pmatrix} + (\tau_0 + \alpha) \begin{pmatrix} 0 & -K \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \phi_1(-1) \\ \phi_2(-1) \end{pmatrix} \\ &\triangleq (\tau_0 + \alpha) A\phi(0) + (\tau_0 + \alpha) B\phi(-1) \end{aligned}$$

and

$$f(\alpha, \phi) \triangleq (\tau_0 + \alpha) \begin{pmatrix} a_2\phi_2^2(-1) + a_3\phi_2^3(-1) + O(\phi_2^4) \\ 0 \end{pmatrix}.$$

By Riesz's representation theorem, there exists a matrix whose components are bounded variation functions $\eta(\theta, \alpha)$ in $\theta \in [-1, 0]$ such that

$$L_\alpha \phi = \int_{-1}^{0} \mathrm{d}\eta(\theta, \alpha)\phi(\theta) \quad \text{for } \phi \in \mathcal{C}. \tag{3.4}$$

In fact, we can choose $\eta(\theta, \alpha) = (\hat{\tau} + \alpha)A\delta(\theta) + (\hat{\tau} + \alpha)B\delta(\theta + 1)$, where

$$\delta(\theta) = \begin{cases} 1, & \theta = 0, \\ 0, & \theta \neq 0. \end{cases}$$

Then (3.4) is satisfied.

For $\phi \in \mathcal{C}$, define

$$A(\alpha)\phi = \begin{cases} \dfrac{\mathrm{d}\phi(\theta)}{\mathrm{d}\theta}, & \theta \in [-1, 0), \\ \displaystyle\int_{-1}^{0} \mathrm{d}\eta(t, \alpha)\phi(t), & \theta = 0, \end{cases}$$

$$R(\alpha)\phi = \begin{cases} 0, & \theta \in [-1, 0), \\ f(\alpha, \phi), & \theta = 0. \end{cases}$$

Then system (3.1) can be rewritten in the following form:

$$\dot{u}_t = A(\alpha)u_t + R(\alpha)u_t, \tag{3.5}$$

where $u_t = u(t + \theta)$ for $\theta \in [-1, 0]$.

For $\psi \in C^1([0, 1], \mathbb{R}^2)$, define

$$A^*\psi(s) = \begin{cases} -\dfrac{\mathrm{d}\psi(s)}{\mathrm{d}s}, & s \in (0, 1], \\ \displaystyle\int_{-1}^{0} \mathrm{d}^{\mathrm{T}}\eta(t, 0)\psi(-t), & s = 0. \end{cases}$$

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For $\phi \in C([-1,0])$ and $\psi \in C([0,1])$, define a bilinear form

$$\langle \psi, \phi \rangle = \bar{\psi}(0)\phi(0) - \int_{-1}^{0}\int_{0}^{\theta} \bar{\psi}(\xi-\theta)\,\mathrm{d}\eta(\theta)\phi(\xi)\,\mathrm{d}\xi,$$

where $\eta(\theta) = \eta(\theta, 0)$. Then A^* and $A(0)$ are adjoint operators. Let $q(\theta)$ and $q^*(s)$ be eigenvectors of A and A^* corresponding to $\mathrm{i}\tau_0\omega_0$ and $-\mathrm{i}\tau_0\omega_0$, respectively. By direct computation, we obtain

$$q(\theta) = (\mathrm{i}\omega_0 + d, 1)^{\mathrm{T}}\mathrm{e}^{\mathrm{i}\omega_0\tau_0\theta},$$
$$q^*(s) = D(1, \mathrm{i}\omega_0 + \mu)\mathrm{e}^{\mathrm{i}\omega_0\tau_0 s},$$

where

$$\bar{D} = \frac{1}{d + \mu + \tau_0 K\mathrm{e}^{-\mathrm{i}\omega_0\tau_0}}.$$

Moreover, $\langle q^*, q\rangle = 1$ and $\langle q^*, \bar{q}\rangle = 0$. Using the same notation as in [6], we first compute the centre manifold C_0 at $\alpha = 0$. Let u_t be the solution of (3.3) when $\alpha = 0$, and then define

$$z(t) = \langle q^*, u_t\rangle, \qquad W(t,\theta) = u_t(\theta) - 2\,\mathrm{Re}\{z(t)q(\theta)\}.$$

On the centre manifold C_0, we have

$$W(t,\theta) = W(z(t), \overline{z(t)}, \theta),$$

where

$$W(z,\bar{z},\theta) = W_{20}(\theta)\frac{z^2}{2} + W_{11}(\theta)z\bar{z} + W_{02}\frac{\bar{z}^2}{2} + W_{30}(\theta)\frac{z^3}{6} + \cdots.$$

z and $\bar{z}$ are local coordinates for the centre manifold C_0 in the direction of q^* and $\bar{q}^*$. Note that W is real if u_t is real. We consider only real solutions. Since $\alpha = 0$, for solution $u_t \in C_0$, we have

$$\begin{aligned} z'(t) &= \mathrm{i}\omega_0\tau_0 z + q^*(\theta)f(W + 2\,\mathrm{Re}\{z(t)q(\theta)\}) \\ &= \mathrm{i}\omega_0\tau_0 z + \bar{q}^*(0)f(W(z,\bar{z},0) + 2\,\mathrm{Re}\{z(t)q(0)\}) \\ &\triangleq \mathrm{i}\omega_0\tau_0 z + \bar{q}^*(0)f_0(z,\bar{z}), \end{aligned} \tag{3.6}$$

where

$$f_0(z,\bar{z}) = f_{z^2}\frac{z^2}{2} + f_{\bar{z}^2}\frac{\bar{z}^2}{2} + f_{z\bar{z}}z\bar{z} + f_{z^2\bar{z}}\frac{z^2\bar{z}}{2} + \cdots.$$

We rewrite this as

$$\dot{z}(t) = \mathrm{i}\omega_0\tau_0 z + g(z,\bar{z}), \tag{3.7}$$

with

$$g(z,\bar{z}) = \bar{q}^*(0)f_0(z,\bar{z}) = g_{20}\frac{z^2}{2} + g_{11}z\bar{z} + g_{02}\frac{\bar{z}^2}{2} + g_{21}\frac{z^2\bar{z}}{2} + \cdots. \tag{3.8}$$

Then we have $g_{20} = \bar{q}^*(0)f_{z^2}$, $g_{11} = \bar{q}^*(0)f_{z\bar{z}}$, $g_{02} = \bar{q}^*(0)f_{\bar{z}^2}$ and $g_{21} = \bar{q}^*(0)f_{z^2\bar{z}}$.

By (3.5) and (3.7), we obtain

$$\left.\begin{aligned}\dot{W} = \dot{u}_t - \dot{z}q - \dot{\bar{z}}\bar{q} &= \begin{cases} AW - 2\,\mathrm{Re}\{\bar{q}^*(0)f_0q(\theta)\}, & \theta \in [-1,0),\\ AW - 2\,\mathrm{Re}\{\bar{q}^*(0)f_0q(\theta)\} + f_0, & \theta = 0,\end{cases}\\ &\triangleq AW + H(z,\bar{z},\theta),\end{aligned}\right\} \tag{3.9}$$

where $f_0 \triangleq f_0(z,\bar{z})$, and

$$H(z,\bar{z},\theta) = H_{20}(\theta)\frac{z^2}{2} + H_{11}(\theta)z\bar{z} + H_{02}(\theta)\frac{\bar{z}^2}{2} + \cdots . \tag{3.10}$$

By expanding the above series and comparing the coefficients, we obtain

$$(A - 2\mathrm{i}\omega_0\tau_0 I)W_{20}(\theta) = -H_{20}(\theta), \qquad AW_{11} = -H_{11}(\theta), \ldots . \tag{3.11}$$

From $u_t = zq(\theta) + \bar{z}\bar{q}(\theta) + W(t,\theta)$, it follows that

$$p(t-1) = \mathrm{e}^{-\mathrm{i}\omega_0\tau_0}z + \mathrm{e}^{\mathrm{i}\omega_0\tau_0}\bar{z} + W_{20}^2(-1)\frac{z^2}{2} + W_{11}^2(-1)z\bar{z} + \cdots ,$$

and from (3.8), we have

$$\begin{aligned} g_{20} &= 2D\tau_0 a_2 \mathrm{e}^{-2\mathrm{i}\omega_0\tau_0},\\ g_{11} &= 2D\tau_0 a_2,\\ g_{02} &= 2D\tau_0 a_2 \mathrm{e}^{2\mathrm{i}\omega_0\tau_0},\\ g_{21} &= 2D\tau_0[2a_2\mathrm{e}^{-\mathrm{i}\omega_0\tau_0}W_{11}^2(-1) + a_2\mathrm{e}^{\mathrm{i}\omega_0\tau_0}W_{20}^2(-1) + 3a_3\mathrm{e}^{-\mathrm{i}\omega_0\tau_0}].\end{aligned}$$

Since, for $\theta \in [-1,0)$,

$$H(z,\bar{z},\theta) = -q^*(0)f_0q(\theta) - q^*(0)\bar{f}_0\bar{q}(\theta) = -g(z,\bar{z})q(\theta) - \bar{g}(z,\bar{z})\bar{q}(\theta),$$

and by comparing coefficients with (3.10), we obtain

$$H_{20}(\theta) = -g_{20}q(\theta) - \bar{g}_{02}\bar{q}(\theta), \qquad H_{11}(\theta) = -g_{11}q(\theta) - \bar{g}_{11}\bar{q}(\theta).$$

By substituting these relations into (3.11) we can derive the following equation:

$$W_{20}'(\theta) = 2\mathrm{i}\omega_0\tau_0 W_{20}(\theta) + g_{20}\mathrm{e}^{\mathrm{i}\omega_0\tau_0\theta} + \bar{g}_{02}\mathrm{e}^{-\mathrm{i}\omega_0\tau_0\theta}.$$

Solving for $W_{20}(\theta)$, we obtain

$$W_{20}^2(-1) = -\frac{g_{20}}{\mathrm{i}\omega_0\tau_0}\mathrm{e}^{-\mathrm{i}\omega_0\tau_0} - \frac{\bar{g}_{02}}{3\mathrm{i}\omega_0\tau_0}\mathrm{e}^{\mathrm{i}\omega_0\tau_0} + E_1^2\mathrm{e}^{-2\mathrm{i}\omega_0\tau_0}.$$

Similarly,

$$W_{11}^2(-1) = \frac{g_{11}}{\mathrm{i}\omega_0\tau_0}\mathrm{e}^{-\mathrm{i}\omega_0\tau_0} - \frac{\bar{g}_{11}}{\mathrm{i}\omega_0\tau_0}\mathrm{e}^{\mathrm{i}\omega_0\tau_0} + E_2^2,$$

where E_1^2 and E_2^2 will be determined as follows. From

$$H(z,\bar{z},0) = -2\,\mathrm{Re}\{\bar{q}^*(0)f_0q(0)\} + f_0,$$

we have

$$H_{20} = -g_{20}q(0) - \bar{g}_{02}\bar{q}(0) + f_{z^2}$$

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and

$$H_{11} = -g_{11}q(0) - \bar{g}_{11}\bar{q}(0) + f_{z(\bar{z})}.$$

From (3.11) and the definition of A, we obtain

$$\left[2\mathrm{i}\omega_0\tau_0 I - \int_{-1}^{0} \mathrm{d}\eta(\theta)\mathrm{e}^{2\mathrm{i}\omega\tau_0\theta}\right]E_1 = f_{z^2}$$

and

$$\int_{-1}^{0} \mathrm{d}\eta(\theta)\mathrm{e}^{2\mathrm{i}\omega\tau_0\theta}E_2 = -f_{z\bar{z}}.$$

Thus,

$$E_1^2 = \frac{2a_2\mathrm{e}^{-2\mathrm{i}\omega_0\tau_0}}{(2\mathrm{i}\omega_0 + \mu)(2\mathrm{i}\omega_0 + d) + K\mathrm{e}^{-2\mathrm{i}\omega_0\tau_0}} \quad \text{and} \quad E_2^2 = \frac{2\tau_0 a_2}{\mu d + K\mathrm{e}^{-2\mathrm{i}\omega_0\tau_0}}.$$

Since each g_{ij} above is determined by the parameters and delays in system (3.1), we can compute the following quantities:

$$\begin{aligned}
C_1(0) &= \frac{\mathrm{i}}{2\omega_0\tau_0}(g_{20}g_{11} - 2|g_{11}|^2 - \tfrac{1}{3}|g_{02}|^2) + \frac{g_{21}}{2},\\
\mu_2 &= -\frac{\operatorname{Re}\{C_1(0)\}}{\operatorname{Re}\lambda'(\tau_0)},\\
\beta_2 &= 2\operatorname{Re}\{C_1(0)\},\\
T_2 &= -\frac{\operatorname{Im} C_1(0) + \mu_2(\operatorname{Im}\lambda'(\tau_0))}{\omega_0}.
\end{aligned}$$

It is well known that μ_2 determines the direction of the Hopf bifurcation: if $\mu_2 > 0$ ($\mu_2 < 0$), then the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions exist for $\tau > \tau_0$ ($\tau < \tau_0$). β_2 determines the stability of the bifurcating periodic solutions. The bifurcating periodic solutions are orbitally asymptotically stable (unstable) if $\beta_2 < 0$ ($\beta_2 > 0$), and T_2 determines the period of the bifurcating periodic solutions: the period increases (decreases) if $T_2 > 0$ ($T_2 < 0$).

From the discussion in § 2 we know that $\operatorname{Re}(\lambda'(\tau_0)) > 0$. We therefore have the following result.

THEOREM 3.1. *The direction of the Hopf bifurcation of system (2.1) at the equilibrium (m^*, p^*) when $\tau = \tau_0$ is supercritical (subcritical) and the bifurcating periodic solutions are orbitally asymptotically stable (unstable) if* $\operatorname{Re}(C_1(0)) < 0$ ($\operatorname{Re} > 0$).

4. Global existence of periodic solutions

In this section we study the global continuation of positive periodic solutions bifurcating from the point (x^*, τ_j), $j = 1, 2, \dots$, $x^* = (m^*, p^*)$ for system (2.1). Through-

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out this section, we closely follow the notation in [32]. We define

$$\begin{aligned} X &= C([-\tau,0],\mathbb{R}^2),\\ \Sigma &= \mathrm{Cl}\{(x,\tau,l)\colon (x,\tau,l)\in X\times\mathbb{R}_+\times\mathbb{R}_+,\\ &\qquad\qquad x \text{ is an } l\text{-periodic solution of system (2.1)}\},\\ N &= \left\{(\hat{x},\tau,l)\colon \hat{x}=(\hat{m},\hat{p}),\ \mu\hat{m}=\frac{1}{1+(\hat{p}/p_0)^n},\ \hat{m}=d\hat{p}\right\},\\ \Delta_{(x^*,\tau,l)}(\lambda) &= \lambda^2+(\mu+d)\lambda+\mu d+K\mathrm{e}^{-\lambda\tau}, \end{aligned}$$

and let $C(x^*,\tau_j,2\pi/\omega_0)$ denote the connected component of $(x^*,\tau_j,2\pi/\omega_0)$ in Σ, where ω_0 and τ_j are defined in (2.6).

Lemma 4.1. *If n is an even number, then all periodic solutions of system (2.1) are positive and uniformly bounded.*

Proof. Let $(m(t),p(t))$ be a non-constant periodic solution of system (2.1), and let $m(t_1)=M$, $m(t_2)=m$ be the maximum and minimum of $m(t)$, respectively. Then $m'(t_1)=m'(t_2)=0$, and by $(2.1)_1$ we have

$$M=\frac{1}{\mu(1+(p(t_1-\tau)/p_0)^n)}\quad\text{and}\quad m=\frac{1}{\mu(1+(p(t_2-\tau)/p_0)^n)}.$$

Note that n is an even number, and hence $(p(t-\tau)/p_0)^n\geqslant 0$. Then $m>0$ and $M\leqslant 1/\mu$. This shows that $0<m(t)\leqslant 1/\mu$.

Let $p(t_3)=P$ and $p(t_4)=p$ be the maximum and minimum of $p(t)$, respectively. Then, $p'(t_3)=p'(t_4)=0$, and by $(2.1)_2$, we have

$$P=\frac{m(t_3)}{d}\quad\text{and}\quad p=\frac{m(t_4)}{d}.$$

It follows that $0<p(t)\leqslant 1/(\mu d)$. The proof is now complete. □

Lemma 4.2. *System (2.1) has no non-trivial τ-periodic solution.*

Proof. For a contradiction, suppose that system (2.1) has a τ-periodic solution. Then the following system of ODEs has a τ-periodic solution:

$$\dot{m}=\frac{1}{1+(p/p_0)^n}-\mu m,\qquad \dot{p}=m-dp. \tag{4.1}$$

If we define

$$P(m,p)\triangleq\frac{1}{1+(p/p_0)^n}-\mu m\quad\text{and}\quad Q(m,p)\triangleq m-dp,$$

then

$$\frac{\partial P}{\partial m}+\frac{\partial Q}{\partial p}=-\mu-d<0.$$

According to the classical Bendixson negative criterion, system (4.1) has no non-constant periodic solutions. This completes the proof. □

LEMMA 4.3. *Assume that one of the following is satisfied:*

(i) $\mu + d > \sqrt{2}\left(1 + \dfrac{(n+1)^2}{4np_0}\left(\dfrac{n-1}{n+1}\right)^{n-1}\right)$;

(ii) $d > 1$ *or* $\mu > \dfrac{(n+1)^2}{4np_0}\left(\dfrac{n-1}{n+1}\right)^{n-1}$.

Then, system (2.1) has no periodic solution of period 4τ. *Moreover, system (2.1) has no periodic solution of period* 2τ.

Proof. Let $x(t) = (m(t), p(t))$ be a 4τ-periodic solution. Set

$$u_k(t) = x(t - (k-1)\tau), \quad k = 1, 2, 3, 4.$$

Then $u(t) = (u_1(t), u_2(t), u_3(t), u_4(t))$ is a periodic solution to the following system of ODEs:

$$\left.\begin{aligned} \dot{m_1} &= \frac{1}{1 + (p_2/p_0)^n} - \mu m_1, \quad \dot{p_1} = m_1 - dp_1, \\ \dot{m_2} &= \frac{1}{1 + (p_3/p_0)^n} - \mu m_2, \quad \dot{p_2} = m_2 - dp_2, \\ \dot{m_3} &= \frac{1}{1 + (p_4/p_0)^n} - \mu m_3, \quad \dot{p_3} = m_3 - dp_3, \\ \dot{m_4} &= \frac{1}{1 + (p_1/p_0)^n} - \mu m_4, \quad \dot{p_4} = m_4 - dp_4. \end{aligned}\right\} \tag{4.2}$$

From lemma 4.1, the periodic orbit of system (4.2) belongs to the region

$$G = \left\{ u \in \mathbb{R}^8 \;\middle|\; \begin{pmatrix} 0 \\ 0 \end{pmatrix} < u_k < \begin{pmatrix} 1/\mu \\ 1/\mu d \end{pmatrix},\ k = 1, 2, 3, 4. \right\} \tag{4.3}$$

If we want to prove that there is no 4τ-periodic solution, it suffices to prove that there is no non-constant periodic solution of system (4.2) in the region G. To do this, we apply the general Bendixson criterion in higher dimensions developed in [9]. It is easy to compute the Jacobian matrix $J(u)$ of system (4.2) for $u \in \mathbb{R}^8$:

$$J(u) = \begin{pmatrix} -\mu & 0 & 0 & f(p_2) & 0 & 0 & 0 & 0 \\ 1 & -d & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu & 0 & 0 & f(p_3) & 0 & 0 \\ 0 & 0 & 1 & d & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu & 0 & 0 & f(p_4) \\ 0 & 0 & 0 & 0 & 1 & d & 0 & 0 \\ 0 & f(p_1) & 0 & 0 & 0 & 0 & -\mu & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & d \end{pmatrix},$$

where

$$f(p_k) = -\frac{np_k^{n-1}}{p_0^n(1 + (p_k/p_0)^n)^2}, \quad k = 1, 2, 3, 4.$$

Then the second additive compound matrix $J^{[2]}(u)$ of $J(u)$ is an $\binom{8}{2} \times \binom{8}{2}$ matrix defined as follows. For any integer $i, j \in N = \{1, 2, \dots, 28\}$, the element in the i

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row and the j column of $J^{[2]}(u)$ is

$$b_{ij} = \begin{cases} -2\mu & \text{if } i=j\in A, \\ -\mu-d & \text{if } i=j\in B, \\ -2d & \text{if } i=j\in C, \\ 1 & \text{if } (i,j)\in D, \\ f(p_1) & \text{if } (i,j)\in\{(6,1),(28,13)\}, \\ -f(p_1) & \text{if } (i,j)\in\{(17,8),(21,9),(24,10),(26,11)\}, \\ f(p_2) & \text{if } (i,j)\in\{(4,19),(5,20),(6,21),(7,22)\}, \\ -f(p_2) & \text{if } (i,j)\in\{(1,9),(2,14)\}, \\ f(p_3) & \text{if } (i,j)\in\{(2,5),(8,11),(17,26),(18,27)\}, \\ -f(p_3) & \text{if } (i,j)\in\{(14,20),(15,23)\}, \\ f(p_4) & \text{if } (i,j)\in\{(4,7),(10,13),(15,18),(19,22)\}, \\ -f(p_4) & \text{if } (i,j)\in\{(23,27),(24,28)\}, \\ 0, & \text{otherwise.} \end{cases}$$

Here,

$$\begin{aligned} A &= \{2,4,6,15,17,24\}, \\ B &= \{1,3,5,7,8,10,12,14,16,18,19,21,23,25,26,28\}, \\ C &= \{9,11,13,20,22,27\}, \\ D &= \{(3,2),(5,4),(7,6),(8,2),(9,3),(9,8),(10,4),(11,5),(11,10), \\ &\qquad (12,6),(13,7),(13,12),(16,15),(18,17),(19,15),(20,16),(20,19), \\ &\qquad (21,17),(22,18),(22,21),(25,24),(26,24),(27,25),(27,26)\}. \end{aligned}$$

Choose a vector form in $\mathbb{R}^{28}$ as

$$|(x_1,x_2,\dots,x_{28})| = \max\{|x_i|,\sqrt{2}|x_j|\},\quad i\in I,\ j\in\frac{N}{I},$$

where

$$N=\{1,2,\dots,28\},\qquad I=\{2,4,6,9,11,13,15,17,20,22,24,27\}.$$

With respect to this norm, we can obtain that the Lozinskiĭ measure $\mu(J^{[2]}(u))$ of the matrix $J^{[2]}(u)$ is given by [1]

$$\mu(J^{[2]}(u)) = \max\{-\mu-d+\sqrt{2}(1+|f(p_k)|)\},\quad k=1,2,3,4. \tag{4.4}$$

By [9, corollary 3.5], system (4.2) has no periodic orbits in G if $\mu(J^{[2]}(u))<0$ for all $u\in G$. By (4.4), we have $\mu(J^{[2]}(u))<0$ if and only if

$$\mu+d>\sqrt{2}(1+|f(p_k)|),\quad k=1,2,3,4. \tag{4.5}$$

Note that $|f(0)|=0$, $\lim_{v\to\infty}|f(v)|=0$. For any $v\geqslant 0$,

$$\frac{\mathrm{d}|f(v)|}{\mathrm{d}v} = \frac{nv^{n-2}[n-1-(n+1)v^n/p_0^n]}{p_0^n(1+v^n/p_0^n)^3} = 0,$$

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if and only if $v = 0$ or $v^n = (n-1)p_0^n/(n+1)$. So we know that $|f(v)|$ takes its minimum and maximum at

$$v = 0 \quad \text{and} \quad v = \sqrt[n]{\frac{n-1}{n+1}p_0^n}, \quad \text{respectively.}$$

The substitution of $v = \sqrt[n]{(n-1)p_0^n/(n+1)}$ into $|f(v)|$ yields

$$\left| f\left(\left(\frac{n-1}{n+1} p_0^n \right)^{1/n} \right) \right| = \frac{(n+1)^2}{4np_0} \left(\frac{n-1}{n+1} \right)^{n-1}.$$

From condition (i), we can obtain (4.5).

If we choose $|(x_1, x_2, \dots, x_{28})| = \max_{1 \leqslant i \leqslant 28}\{|x_i|\}$ as the vector norm, the corresponding Lozinskiĭ measure $\mu(J^{[2]}(u))$ of the matrix $J^{[2]}(u)$ is as follows [1]:

$$\mu(J^{[2]}(u)) = \max\{-2d + 2, -2\mu + 2|f(p_k)|\}, \quad k = 1, 2, 3, 4.$$

In order to obtain $\mu(J^{[2]}(u)) < 0$, we should take

$$d > 1 \quad \text{or} \quad \mu > |f(p_k)|, \quad k = 1, 2, 3, 4,$$

and this can be satisfied by condition (ii). □

THEOREM 4.4. *Suppose that n is an even number,*

$$\mu d < K < \sqrt{\mu d}(\mu + d), \tag{H2}$$

and that either (i) or (ii) of lemma 4.3 is satisfied. Then, for each $\tau > \tau_j$, $j = 0, 1, 2, \dots$, system (2.1) has at least $j+1$ non-constant, positive periodic solutions, where τ_j is defined by (2.6).

Proof. It is sufficient to prove that the projection of $C(x^*, \tau_j, 2\pi/\omega_0)$ onto τ-space includes $[\tau_j, \infty)$ for each $j \geqslant 0$. We gave the characteristic matrix of system (2.1) at an equilibrium (m^*, p^*) at the beginning of this section.

By lemmas 4.1 and 4.3, there exist $\varepsilon > 0$, $\delta > 0$ and a smooth curve $\lambda\colon (\tau_j - \delta, \tau_j + \delta) \to C$, such that

$$\Delta(\lambda(\tau)) = 0, \qquad |\lambda(\tau) - \mathrm{i}\omega_0| < \varepsilon,$$

for all $\tau \in [\tau_j - \delta, \tau_j + \delta]$ and

$$\lambda(\tau_j) = \mathrm{i}\omega_0, \qquad \left.\frac{\mathrm{d}\,\mathrm{Re}(\lambda(\tau))}{\mathrm{d}\tau}\right|_{\tau=\tau_j} > 0.$$

Define $l_j = 2\pi/\omega_0$, and let

$$\Omega_\epsilon = \{(0, l)\colon 0 < u < \varepsilon,\ |l - l_j| < \varepsilon\}.$$

Obviously, if $|\tau - \tau_j| \leqslant \delta$ and $(u, l) \in \partial\Omega_\varepsilon$ such that $\Delta_{(x^*,\tau,l)}(u + 2\pi\mathrm{i}/l) = 0$, then $\tau = \tau_j$, $u = 0$, $l = l_j$. Set

$$H^{\pm}\left(x^*, \tau_j, \frac{2\pi}{\omega_0}\right)(u, l) = \Delta_{(x^*,\tau_j\pm\delta,l)}\left(u + \frac{2\pi\mathrm{i}}{l}\right).$$

We obtain the crossing number

$$\gamma_1\left(x^*,\tau_j,\frac{2\pi}{\omega_0}\right) = \deg_B\left(H^-\left(x^*,\tau_j,\frac{2\pi}{\omega_0}\right),\Omega_\varepsilon\right) - \deg_B\left(H^+\left(x^*,\tau_j,\frac{2\pi}{\omega_0}\right),\Omega_\varepsilon\right) = -1.$$

We conclude that

$$\sum_{(\hat{x},\tau,l)\in C(x^*,\tau_j,2\pi/\omega_0)} \gamma_1(\hat{x},\tau,l) < 0.$$

By [32, theorem 3.3], $C(x^*,\tau_j,2\pi/\omega_0)$ is unbounded.

Lemma 4.1 implies that the projection of $C(x^*,\tau_j,2\pi/\omega_0)$ onto the x-space is bounded. Similarly to lemma 4.2, one can prove that system (2.1) with $\tau = 0$ has no non-constant periodic solutions. Hence, the projection of $C(x^*,\tau_j,2\pi/\omega_0)$ onto the τ-space is bounded below.

From the definition of τ_j in (2.6) and (H2), we know that

$$\frac{\pi}{2} < \tau_0\omega_0 < \pi, \quad 2\pi < \tau_j\omega_0 < (2j+1)\pi, \quad j \geqslant 1.$$

Hence,

$$2\tau_0 < \frac{2\pi}{\omega_0} < 4\tau_0, \quad \frac{\tau_j}{j+1} < \frac{2\pi}{\omega_0} < \tau_j, \quad j \geqslant 1.$$

From lemmas 4.2 and 4.3 we know that $2\tau < l < 4\tau$ if $(x,\tau,l) \in C(x^*,\tau_0,2\pi/\omega_0)$, and $\tau/(j+1) < l < \tau$ if $(x,\tau,l) \in C(x^*,\tau_j,2\pi/\omega_0)$ for $j \geqslant 1$. So, in order for $C(x^*,\tau_0,2\pi/\omega_0)$ to be unbounded, its projection onto the τ-space must be unbounded. So, for each $\tau > \tau_j$, system (2.1) has $j+1$ non-constant, positive periodic solutions. This completes the proof. □

Remark 4.5. From the proof of theorem 4.4, we know that the first global Hopf branch contains periodic solutions of the period between 2τ and 4τ. These are the slowly oscillating periodic solutions. For $j \geqslant 1$, the τ_j branches contain fast-oscillating periodic solutions because the periods are less than τ.

Remark 4.6. For $j \geqslant 1$,

$$\frac{\tau_j}{j+1} < \frac{2\pi}{\omega_0} < \tau_j$$

automatically holds. The bounds on the period l for $(x,\tau,l) \in C(x^*,\tau_j,2\pi/\omega_0)$ hold without the result of lemma 4.3. Thus, the global extension of the τ_j branches for $j \geqslant 1$ can be proved without the restrictions (i) and (ii) in lemma 4.3 and (H2).

5. Computer simulation

In order to illustrate the analytical results obtained, we will consider a particular case of system (2.1). Since the reasonable estimates for p_0, n and τ are $10 \leqslant p_0 \leqslant 100$, $2 \leqslant n \leqslant 10$ and $15\,\text{min} \leqslant \tau \leqslant 20\,\text{min}$ [14], we choose the coefficients as follows: $\mu = 0.16$, $d = 0.1$, $n = 4$ and $p_0 = 40$. Then system (2.1) can be expressed as follows:

$$\dot{m} = \frac{1}{1+(p(t-\tau)/40)^4} - 0.16m, \quad \dot{p} = m - 0.1p. \tag{5.1}$$

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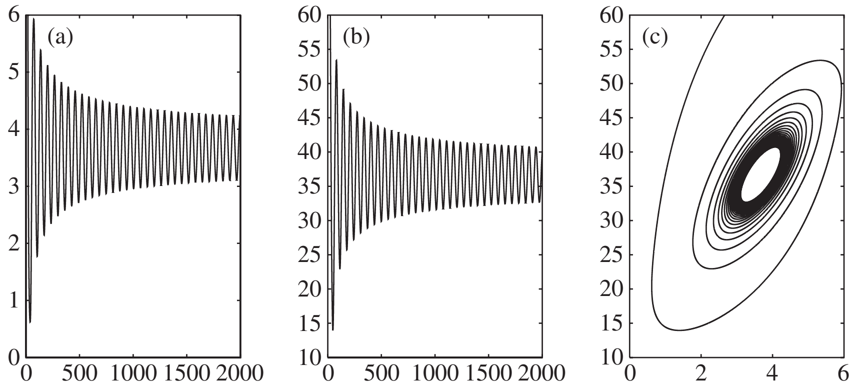

Figure 2. Waveform and phase plots for system (2.1) with $\mu = 0.16$, $d = 0.1$, $n = 4$, $p_0 = 40$ and $\tau_0 \doteq 18.2674 < \tau = 18.5 < 20$. (a) m waveform; (b) p waveform; (c) $m - p$ phase plots.

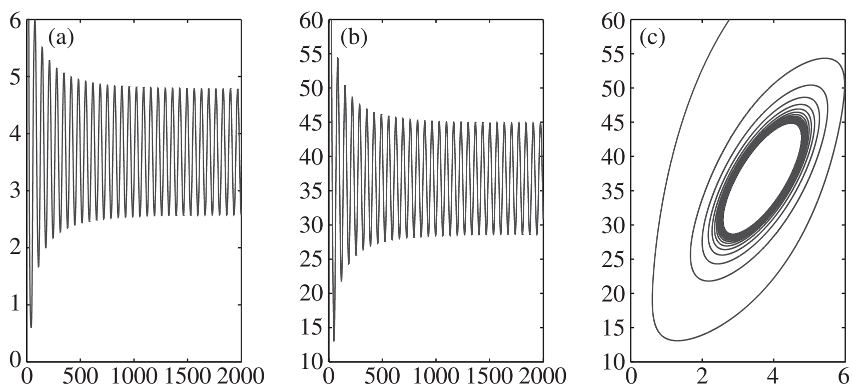

Figure 3. Waveform and phase plots for system (2.1) with $\mu = 0.16$, $d = 0.1$, $n = 4$, $p_0 = 40$ and $\tau = 20$. (a) m waveform; (b) p waveform; (c) $m - p$ phase plots.

The equilibrium is given by $(3.6654, 36.6543)$, and (H1) is satisfied. We can obtain

$$\tau_0 \doteq 18.2674, \quad \operatorname{Re} \lambda'(\tau_0) = 9.2284 \times 10^{-4}, \quad g_{20} \doteq 0.0014 + 0.0081\mathrm{i},$$
$$g_{11} \doteq 0.0025 - 0.0079\mathrm{i}, \quad g_{02} \doteq -0.0058 + 0.0059\mathrm{i}, \quad g_{21} \doteq -0.0031 + 0.0038\mathrm{i}.$$

So, we have

$$C_1 \doteq -0.0016 + 0.0019\mathrm{i}, \qquad \mu_2 \doteq 1.7079, \qquad \beta_2 \doteq -0.0032, \qquad T_2 \doteq -0.0191.$$

Hence, we can conclude that the bifurcation occurs when τ crosses τ_0 to the right-hand side, the bifurcating periodic solutions are orbitally asymptotically stable and the period decreases. Figure 2 shows a simulation of the model with $\tau = 18.5$. We can also verify that (H2) and lemma 4.3(ii) are satisfied. These are illustrated in figure 3.

Remark 5.1. Model (5.1) exhibits pronounced oscillations in HES1 mRNA and HES1 protein expression when $\tau > \tau_0$, and this situation will continue in the reasonable region of τ. That is, the sustained oscillation can be induced if $\tau \in (\tau_0, 20]$.

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